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EXAMINER

MYERS, CARLA J

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1634

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

8A

**Office Action Summary**

Application No.

09/424,629

Applicant(s)

FOOTE ET AL.

Examiner

Carla Myers

Art Unit

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**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-18 and 24-35 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 24-35 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. ____   |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date ____  | 6) <input type="checkbox"/> Other: ____                                     |

### **DETAILED ACTION**

1. The allowability of claims 1-18 and 24-35 is withdrawn. As indicated in the letter of April 20, 2004, prosecution in this application is being re-opened. Upon further consideration, the following new grounds of rejection are being applied. This action is made non-final.

#### **Claim Rejections - 35 USC § 112**

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18, and 31-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18, and 33-35 are indefinite over the recitation of "is indicative of a difference of one or more nucleotides in said tested nucleic acid molecule." It is unclear as to what is intended to be encompassed by a difference in one or more nucleotides. Additionally, the claims are drawn to methods for detecting a difference of one or more nucleotides between a nucleic acid to be tested and a reference nucleic acid. Yet, the final step of the recited method is one which indicates only a "difference in one or more nucleotides in said tested nucleic acid." The claims should be amended to clarify that the presence of an altered peak is indicative of a difference of one or more nucleotides in the test nucleic acid molecule relative to (or compared to) the reference nucleic acid molecule.

Claim 8 is indefinite and confusing over the recitation of "further separation (PSD)." It is unclear as to whether the claim is intended to include any means for separation or if the claim is intended to be limited to methods in which the separation is by PSD.

Claims 8-9 and 11-18, 31 and 32 are indefinite over the recitation of "subjecting fragmentation products." While the claims previously refer to oligonucleotide fragments, the claims do not previously refer to fragmentation products. Therefore, it is not clear as to whether the fragmentation products are considered to be the same as or different from the oligonucleotide fragments and it is unclear as to how the step of subjecting the fragmentation products to further separation relates to the remainder of the claim.

Claims 14, 17 and 18 are indefinite because they refer to "A method according to claim 10." However, claim 10 is drawn to a computer program and not to a method.

Claim 16 is indefinite over the recitation of "the uracil specific cleavage" because this phrase lacks proper antecedent basis. It appears that claim 16 should depend from claim 15 rather than claim 14.

Claims 33-35 are indefinite over the recitation of "does not result in a change in a cleavage site." The claims previously refer to a method or computer system for controlling a method, wherein the method identifies or locates a mutation that "does not result in a change of a cleavage site by a restriction enzyme." Yet, the final step of the method is one which detects a larger genus of mutations that do not result in a change to any type of a cleavage site. Accordingly, it is not clear as to whether the recited methods are limited to only those methods which identify or locate a mutation that does

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not result in a change of a cleavage site by a restriction enzyme or if the claims encompass methods which identify or locate a mutation that does not result in a change to any type of cleavage site.

### **Claim Rejections - 35 USC § 103**

3 . Claims 1-7, 10, 17 18, 24-30, 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb (U.S. Patent No. 5,869,242) in view of Koster (U.S. Patent 6,500,621).

Kamb teaches methods for detecting a mutation, polymorphism or other type of nucleotide variation in a nucleic acid molecule. In the method of Kamb, differences in the nucleotide composition and / or length of a nucleic acid molecule are identified using MALDI MS to compare the mass spectra of the nucleic acid to a reference nucleic acid (see column 2). In particular, Kamb (column 2, lines 48-59) teaches that variations in a nucleic acid sequence can be detected by a method comprising preparing "amplified DNA from a patient's sample in the region of a known mutation. The amplified DNA is then analyzed in a mass spectrometer to determine the mass of the amplified fragment. The mass spectrum obtained is compared to the mass spectrum of fragments obtained from known samples of either wild-type genes or genes containing the known mutation. These known spectra are referred to as "signature" spectra. A simple comparison of the sample spectrum vs. signature spectra will reveal whether the patient's DNA contains a mutation." Kamb further teaches that a "variation of the above technique may also be used to analyze for polymorphisms. In this variation the fragments of nucleic acid are digested via any one of several techniques to smaller fragments which may range from

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one base up to approximately 50 bases. The resulting mix of fragments is then analyzed via mass spectrometry. The resulting spectrum contains several peaks and is compared with signature spectra of samples known to be wild-type or to contain a known polymorphism." (see column2, line 65 to column 3, line 6).

Accordingly, Kamb teaches that any art conventional method of specific digestion can be used to detect the presence of a nucleotide variation. In one embodiment of the method, Kamb teaches that the digestion step may be performed with a restriction endonuclease (see, for example, column 6). In another embodiment, Kamb teaches that a ribonuclease may be used to detect the presence of nucleotide variation in a sample RNA. Specifically, Kamb (column 10) teaches digestion of RNA using ribonuclease T1, which hydrolyzes RNA on the 3' side of G residues. Ribonuclease T1 digestion is considered to be "single-base-specific cleavage" since the enzyme recognizes and cleaves specifically between the guanosine 3'-phosphate residue and the 5'OH residue of adjacent nucleotides. While Kamb teaches that the oligonucleotides and oligonucleotide fragments present following the cleavage reaction are analyzed using MS, and particularly MALDI MS, Kamb does not specifically teach analyzing the oligonucleotides using MALDI-TOF MS.

However, Koster teaches methods for detecting the presence of a mutation or polymorphism wherein the methods comprise cleaving a nucleic acid with one or specific endonucleases to form a mixture of fragments and comparing the molecular weights of test fragments with the molecular weights of wildtype and mutant fragments using MALDI-TOF MS (see column 18, lines 54-58). Koster (column 3) teaches that

"MALDI mass spectrometry, in contrast, can be particularly attractive when a time-of-flight (TOF) configuration is used as a mass analyzer...Since, in most cases, no multiple molecular ion peaks are produced with this technique, the spectra, in principle, look simpler compared to ES mass spectrometry." Koster (column 28) teaches that MALDI TOF MS can distinguish between oligonucleotides that differ in length by one nucleotide and provides a fast and reliable means for analyzing nucleic acids.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practice the method of Kamb using the MALDI TOF MS technique to analyze the digested and undigested oligonucleotides because Koster teaches that MALDI TOF MS provides an effective and rapid means for detecting and distinguishing between oligonucleotide fragments based on their size and composition and MALDI TOF MS provides a simpler spectra to interpret as compared to other types of mass spectrometry.

With respect to claim 2, Kamb (column 10) teaches that the sample RNA to be used for analysis is prepared by amplifying fragments of DNA, cloning the fragments into vectors containing RNA polymerase promoters and synthesizing RNA transcripts. At column 4 (lines 2-8), Kamb teaches that DNA amplification is accomplished by PCR.

With particular respect to claims 6, 7, 31 and 33, Kamb (see, for example, column 2, lines 53-64; column 5, lines 5-61) teaches that the presence of a nucleotide variation can be detected by direct analysis of oligonucleotides or by base-specific digestion of oligonucleotides and Kamb teaches that the method is applicable to simultaneously detecting multiple variations. Accordingly, it would have been obvious to

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one of ordinary skill in the art at the time the invention was made to have practiced the method of Kamb so as to have detected both variations that result in a change in a cleavage site and variations which do not result in a change in a cleavage site in order to have allowed for the analysis of a wider variety of variations and to have allowed for the detection of multiple variations in the oligonucleotide being analyzed or to have identified variations that do not lead to a change in a cleavage site.

Further, Kamb (column 4, lines 36-41) states that in one embodiment, it is beneficial "to incorporate deoxyuridine into amplified DNA. This is useful for producing small fragments by later digesting the amplified DNA with uracil-N-glycosidase." Kamb discusses the benefit of analyzing smaller fragments of nucleic acids. For instance, at column 3 (lines 49-55), Kamb states that "There is no need to analyze fully the complete gene sequence of a gene associated with a disease...Rather one can use a method which is exquisitely precise in determining the total composition of fragments. Mass spectroscopy is one such method which yields very precise results and is applicable to short nucleotide fragments. " Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated deoxyuridine into the sample nucleic acid during PCR, and to have cleaved the PCR products using uracil-N-glycosylase prior to performing MALDI TOF MS in order to have achieved the benefits stated by Kamb of generating shorter fragments that could be readily analyzed by mass spectrometry and which would allow for the detection of the presence of a mutation or polymorphism in the nucleic acid sample.

With respect to claims 10, 17, 18 and 34, Kamb does not specifically teach a computer program to control the method of detecting a difference in one or more nucleotides of a sample nucleic acid as compared to a reference nucleic acid. However, Kamb (column 11) does teach that "(m)ass spectrometers are presently available which have target slides with 64 sample spots that can be deposited by a robot" and that use of such an automated system provides for the rapid analysis of nucleic acid samples. Further, Koster (column 2, lines 40-46) states that "Due to the apparent analytical advantages of mass spectrometry in providing high detection sensitivity, accuracy of mass measurements, detailed structural information by CID in conjunction with MS/MS configuration and speed, as well as on-line data transfer to a computer, there has been considerable interest in the use of mass spectrometry for the structural analysis of nucleic acids." Additionally, the use of computer programs to control methods and store data obtained from nucleic acid analysis, particularly MALDI MS analysis, was conventional in the art at the time the invention was made. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a computer program to control the method of detecting a nucleotide variation in a nucleic acid sample in order to have provided a convenient and rapid means for storing and analyzing the data obtained from the detection method and / or for automating the detection method.

4. Claims 1-7, 10, 17, 18, 24-30, 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb (U.S. Patent No. 5,869,242) in view of Koster (U.S. Patent 6,500,621) and further in view of McCarthy (WO 97/03210).

This rejection is based on the interpretation that the claims encompass methods in which uracil-N-glycosylase is used to directly detect the presence of a mutation and is used to cleave the sample nucleic acid at a site of nucleotide variation.

The teachings of Kamb and Koster are presented above. In particular, in combination Kamb and Koster teach a method to detect the presence of a nucleotide variation in a sample nucleic acid wherein the method comprises base specific digestion of the sample nucleic acid and analysis of the digested nucleic acids by MALDI TOF MS in order to compare the lengths and compositions of digested sample nucleic acids with reference nucleic acids. Kamb teaches that digestion may be performed "via any one of several techniques." Kamb (column 4, lines 36-41) also states that in one embodiment, it is beneficial "to incorporate deoxyuridine into amplified DNA. This is useful for producing small fragments by later digesting the amplified DNA with uracil-N-glycosidase." Kamb does not specifically teach using uracil-N-glycosidase to directly detect the presence of a mutation that alters a cleavage site.

McCarthy (see, for example, pages 8 and 13) teaches a method for detecting the presence of a mutation in a nucleic acid. In the method of McCarthy, PCR is performed in the presence of deoxyuridine triphosphate (dUTP) so as to generate an amplification product containing dUTP, the amplification product is treated with the enzyme uracil-N-glycosylase in order to cleave the nucleic acid. The enzyme cleaves the nucleic acid between the base uracil and the sugar moiety of the DNA to generate an apyrimidinic site, which is subsequently cleaved to generate DNA fragments. Cleavage occurs only if dUTP has become incorporated into the nucleic acid molecule. In this way, the

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method is diagnostic for the presence of a T residue at a specific position in the DNA sequence and thereby assaying the cleavage products can be used to detect the presence of a mutation to a T residue in the nucleic acid. McCarthy (page 17) teaches that the DNA fragments are analyzed by "existing DNA sizing methods such as polyacrylamide gel electrophoresis, agarose gel electrophoresis or high performance liquid chromatography (HPLC)."

In view of the teachings of McCarthy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamb so as to have performed the cleavage reaction using uracil-N-glycosylase. The ordinary artisan would have been motivated to have used uracil-N-glycosylase in place of ribonuclease T1 or another cleavage reagent because McCarthy teaches that uracil-N-glycosylase can be used to specifically detect the presence or absence of a T residue at a specific location in a nucleic acid and thereby use of uracil-N-glycosylase in the method of Kamb would have provided an effective means for analyzing DNA samples for the presence of a mutation involving thymine.

5. Claims 8, 9, 11-16, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb in view of Koster, or Kamb in view of Koster and further in view of McCarthy, as applied in paragraphs 3 and 4 above respectively, each further in view of Vestal (U.S. Patent NO. 6,057,543).

The teachings of Kamb in view of Koster and Kamb in view of Koster and McCarthy are presented above. The combined references do not teach further separation of the DNA fragments by post source decay.

Vestal teaches the use of post source decay in combination with MALDI TOF MS to analyze nucleic acids. Vestal states that "by suitable adjustment of the mirror potentials these fragment ions may be focused to produce a high quality post-source decay (PSD) spectrum which can be used to determine molecular structure. It is therefore a principal object of this invention to improve the performance of time-of-flight mass spectrometers, particularly in regard to applications involving production of ions from surfaces, by improving resolution, increasing mass accuracy, increasing signal intensity, and reducing background noise. It is another object to reduce the matrix ion signal in MALDI time-of-flight mass spectrometers. Another objective is to provide TOF mass spectrometers suitable for fast sequencing of biopolymers such as nucleic acids, peptides, proteins, and polynucleotides by the analysis of chemically or enzymatically generated ladder mixtures. Still another objective is to utilize fast fragmentation processes for obtaining structural information on biomolecules such as oligonucleotides, carbohydrates, and glycoconjugates."

In view of the teachings of Vestal, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamb so as to have further separated the DNA fragments by post source decay in order to have improved the resolution and accuracy of the detection method and to have allowed for further analysis of the molecular structure of the DNA fragments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00


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PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Carla Myers  
April 28, 2004

  
CARLA J. MYERS  
PRIMARY EXAMINER